IRB Proposal
2/18/2011

Title: Coronary Angiography and the Progression of Kidney Disease in Heart Transplant Recipients

Nathaniel Smilowitz, M.D., Co-Investigator

Background & Rationale:

Over 3,400 orthotopic heart transplants (OHT) are performed annually worldwide, with a transplant half-life of 13 years for recipients who survive the first post-operative year.[1, 2] Progressive renal dysfunction is common among OHT recipients, with moderate or severe renal disease observed in 50% of those who survive to one year; at 5 years there is an 11% cumulative incidence of severe renal dysfunction and by 10 years only 60% of transplant recipients remain free from severe chronic kidney disease.[1, 3-5] Age at transplant, female sex, pre-transplant kidney disease, diabetes, hypertension, and immunosuppression with calcineurin inhibitors have been implicated as risk factors for worsening renal disease.[5, 6] Renal disease following orthotopic heart transplant is associated with significant morbidity and all-cause and cardiac mortality.[1, 3, 4, 6]

Transplant allograft vasculopathy is a leading cause of death in transplant recipients, leading to rigorous surveillance with coronary angiography.[7] Contrast-induced nephropathy, a syndrome of acute renal failure after the administration of iodinated contrast, is a major complication of coronary angiography and is associated with significant in-hospital mortality and poor long-term survival. In patients with pre-existing renal disease and significant risk factors, contrast administration can also precipitate a chronic deterioration of renal function.[8] The role of contrast-induced nephropathy and its contribution to the progression of renal failure in the adult orthotopic heart transplant population has not been studied.

Hypothesis:

Administration of large volumes of contrast during surveillance coronary angiography in heart transplant patients accelerates the development and progression of CKD.

Study Design:

A retrospective, case-control study of consecutive adults who received orthotopic heart transplants at New York Presbyterian Hospital Columbia University Medical Center in 2004-2005 will be performed. We plan to identify patients who developed moderate or severe renal dysfunction (eGFR<60 mL/min/1.73m^2) or progression of renal disease (a ≥25% decrease in eGFR) within 3 months following a surveillance coronary angiogram during the first five-year post-transplant period. Cases will be excluded if progression of CKD was unrelated to contrast exposure, as defined by renal dysfunction prior to or within the first year post-transplant, prior to contrast exposure from coronary angiography, or linked to an acute event without contrast exposure (rejection, hospitalization, or surgery). The control group, consecutive OHT recipients who did not develop moderate renal dysfunction or progression of renal disease during the first five

years post-transplant, will be matched to cases by duration of time post-transplant. Total contrast exposure will be compared between these two patient groups.

To identify cases for the study, serial estimates of post-transplant kidney function will be tabulated over a five-year post-transplant period for all OHT recipients. Procedural data from coronary angiography will be obtained, including contrast volume, case duration, catheter/sheath size, and the presence or absence of allograft vasculopathy.

Additional data to be collected for each case will include age at transplant, sex, pre-existing cardiovascular risk factors including HTN, dyslipidemia, diabetes, peripheral vascular disease, baseline pre-transplant kidney function (eGFR), hepatitis serologies, CMV serology, etiology of pre-transplant cardiomyopathy, method of induction immunosuppression, maintenance immunosuppression drug regimen and dosing, calcineurin inhibitor serum levels, episodes of rejection (grade, management approach), and angiotensin converting enzyme inhibitor, angiotensin receptor blocker, and trimethoprim/sulfamethoxazole use post-transplant.

Statistical Analysis
We plan to compare total iodinated contrast volume administered post-transplant among cases prior to the development of moderate to severe chronic kidney disease and controls during a similar post-transplant timeframe. Mean values will be compared by the unpaired students T-test for normally distributed continuous data, and the Fisher's exact or the chi-square test for categorical variables. All comparisons will be two-tailed, P-values of <0.05 will be considered statistically significant for all tests. Logistic regression will be performed to control for covariates affecting renal function, including immunosuppression method and dose.

Power calculation: NYPH-CUMC performs approximately 75 to 100 adult cardiac transplants each year, with an average survival of approximately 10 years. We expect 200 OHT recipients will be screened; we expect there will be 125 cases without moderate or severe renal dysfunction at baseline. Approximately 25 cases will have new-onset moderate to severe renal dysfunction following coronary angiography, and 50 applicable controls with good renal function during the matched timeframe should be available. In a previous study, the average contrast media volume delivery during routine, ambulatory diagnostic catheterization at CUMC was 105 mL ± 40 mL (unpublished data). Therefore, recruitment of 25 study cases and 50 controls will allow for discrimination of a 28 mL difference in contrast volume between the two groups with an alpha of 0.05 and at 80% power.

Study Procedure
Retrospective chart review will be performed.

Study Drugs or Devices
Not applicable

Study Questionnaire

Not applicable

Study Subjects
Case Inclusion Criteria:

1. Consecutive adult (age ≥ 18) orthotopic heart transplant recipients in 2004-2005.
2. Survival post-transplant >1 year
3. Baseline MDRD eGFR>60 mL/min/1.73m^2 (prior to 1st coronary angiogram post-transplant)
4. Development of moderate or severe renal dysfunction (eGFR>60 mL/min/1.73m^2) or ≥25% decline in eGFR within 3 months following coronary angiography during the first 5 years post-transplant

Control Inclusion Criteria:

1. Consecutive adult (age ≥ 18) orthotopic heart transplant recipients in 2004-2005.
2. Survival post-transplant ≥5 years
3. Baseline eGFR > 60 mL/min/1.73m^2 (prior to 1st coronary angiogram post-transplant)
4. No ≥25% decline in eGFR or development of moderate or severe renal insufficiency during the 5-year timeframe.

Exclusion Criteria:

1. Baseline renal dysfunction with eGFR<60 mL/min/1.73m^2 (MDRD)
2. Development of moderate or severe renal dysfunction unrelated to coronary angiography:
    a. Prior to transplant
    b. Within the first year post-transplant
    c. Prior to any contrast exposure
    d. Temporally linked to an acute event without contrast exposure (acute rejection, inpatient hospitalization, surgery
3. Inadequate clinical documentation or poor follow up

Women and minorities will be included in this study to achieve a sample representative of the heart transplant recipients at NYPH/CUMC.

Recruitment of Subjects:
Subjects will be recruited via a retrospective review of existing hospital documentation among orthotopic heart transplant recipients. Patients will not be contacted or recruited to participate in this study.

Confidentiality of Study Data:
Data will be stripped of personal identifiers. Each case will be assigned a unique study identifier. Only study investigators will have access to study data.

Potential Conflicts of Interest
None

Study Location:
New York-Presbyterian Hospital: Columbia University Medical Center

Potential Risks:
There are no potential risks to patients included in this retrospective study.

Potential Benefits:
There are no immediate or direct benefits to patients included in the study. However, study results may guide management of contrast administration during post-transplant surveillance coronary angiography.

Alternative Therapies:
Not Applicable

Compensation to Subjections:
None

Costs to Subjects:
None

Minors as Research Subjects:
No minors will be included in the study.

Radiation or Radioactive Substances
Radiation exposure occurs to all patients undergoing surveillance coronary angiography. No additional radiation exposure will occur as a result of this retrospective case-control study.

References

1. Taylor DO, Stehlik J, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Heart Transplant Report-2009. J Heart Lung Transplant 2009;28:1007-22.
2. Roussel JC, Baron O, Perigaud C, et al. Outcome of heart transplants 15 to 20 years ago: graft survival, post-transplant morbidity, and risk factors for mortality. J Heart Lung Transplant 2008;27:486-93.
3. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931-40.
4. Arora S, Andreassen A, Simonsen S, et al. Prognostic importance of renal function 1 year after heart transplantation for all-cause and cardiac mortality and development of allograft vasculopathy. Transplantation 2007;84:149-54.
5. Delgado JF, Crespo-Leiro MG, Gomez-Sanchez MA, et al. Risk factors associated with moderate-to-severe renal dysfunction among heart transplant patients: results from the CAPRI study. Clin Transplant 2010;24:E194-200.
6. Al Aly Z, Abbas S, Moore E, Diallo O, Hauptman PJ, Bastani B. The natural history of renal function following orthotopic heart transplant. Clin Transplant 2005;19:683-9.
7. Schmauss D, Weis M. Cardiac allograft vasculopathy: recent developments. Circulation 2008;117:2131-41.
8. Pucelikova T, Dangas G, Mehran R. Contrast-induced nephropathy. Catheter Cardiovasc Interv 2008;71:62-72.
9. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997;103:368-75.
10. Rihal CS, Textor SC, Grill DE, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002;105:2259-64.